



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

0 149 847
A2

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 84116353.8

(51) Int. Cl.: A 61 K 31/045
A 61 K 31/66

(22) Date of filing: 27.12.84

(30) Priority: 26.12.83 JP 244227/83
26.12.83 JP 244228/83
26.12.83 JP 244229/83
26.12.83 JP 244230/83

(43) Date of publication of application:
31.07.85 Bulletin 85/31

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI NL SE

(71) Applicant: Eisai Co., Ltd.
6-10, Koishikawa 4-chome Bunkyo-ku
Tokyo 112(JP)

(72) Inventor: Yamatsu, Ise
3605-699, Kashiiwada Ushikumachi
Inashiki-gun Ibaragi(JP)

(72) Inventor: Suzuki, Takeshi
56-107, Sakae-cho 1 chome Ushikumachi
Inashiki-gun Ibaragi(JP)

(72) Inventor: Abe, Shinya
40-2, Ohaza-Shiroyama Kukizakimura
Inashiki-gun Ibaragi(JP)

(72) Inventor: Nakamoto, Kouji
712-91, Itaya-cho Nakanuki
Tsuchiura-shi Ibaragi(JP)

(72) Inventor: Kajiwara, Akiharu
29-4, Higashi-Arai Yatabemachi
Tsukuba-gun Ibaragi(JP)

(72) Inventor: Katayama, Kouichi
2-33, Umezono Sakuramura
Niihari-gun Ibaragi(JP)

(72) Inventor: Tsunoda, Hajime
10-4, Toukoudai 1 chome Toyosatomachi
Tsukuba-gun Ibaragi(JP)

(72) Inventor: Murakami, Manebu
6-8, Toukoudai 1 chome Toyosatomachi
Tsukuba-gun Ibaragi(JP)

(72) Inventor: Ono, Hideki
23-30, Umezono 2 chome Sakuramura
Niihari-gun Ibaragi(JP)

(72) Inventor: Yamada, Kouji
15-19, Toride 2 chome
Toride-shi Ibaragi(JP)

(74) Representative: Hansen, Bernd, Dr.rer.nat. et al,
Hoffmann, Eitle & Partner Patentanwälte Arabellastrasse
4
D-8000 München 81(DE)

A2
847 847

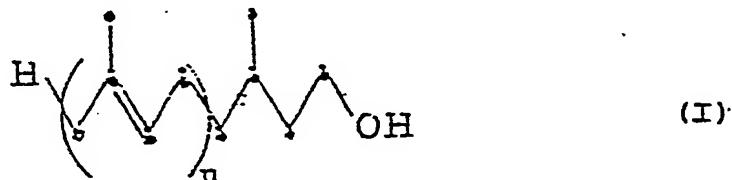
EP 0 149

(64) Therapeutic and preventive agent containing dolichol.
(67) Dolichol or phosphate thereof is useful as a therapeutically treating and preventive agent, in particular, for hyperuricuria, hyperlipemia, diabetes and hepatic diseases.

Therapeutic and Preventive Agent
containing Dolichol

The invention relates to a therapeutically treating and preventive agent containing as a pharmaceutically effective component dolichol or a phosphate thereof. The invention agent is 5 effective to treat and prevent, in particular, hyperuricuria, hyperlipemia, arteriosclerosis, diabetes and hepatic diseases; and then improve lipometabolism.

Dolichol is a polyprenol having the following 10 structure and occurs in yeasts and mammals:



15 wherein n represents an integer of 14 to 24.

Dolichol is characterized by the presence of two trans-isoprene units and a cis-isoprene unit attached thereto and a saturated alcohol-terminal

(*α*-terminal) isoprene unit. Dolichol is supposed to play an important role in life conservation of organisms and expected to be available as an active ingredient for various pharmaceuticals.

5 Under these circumstances, we have examined the pharmaceutical availability of dolichol for a long time. As a result of our researches, we have found that dolichol is unexpectedly effective to treat and prevent hyperuricuria such as gout,
10 hyperlipemia, arteriosclerosis, diabetes and hepatic diseases; and then improve lipometabolism.

Dolichol to be used in the embodiments of the present invention may be prepared by any convenient method. That is to say, it may be extracted, for
15 example, from swine liver (cf. F.W. Burgos et al., Biochemical Journal, 88, 470(1963)) or swine pancreas (cf. Japanese Patent Application No. 12622/1983). Alternately, it may be prepared by fermentation with microorganisms. Furthermore it may
20 be chemically synthesized.

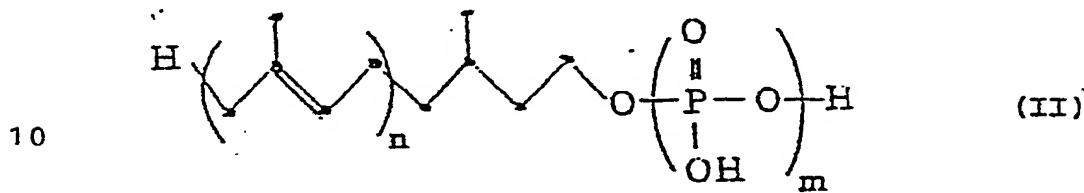
The aforementioned chemical structure indicates that dolichol may occur in various forms depending on n. Dolichol being used in the present invention may be either a single compound wherein
25 n is a particular integer (e.g. n is 19) or a mixture of compounds wherein n represents various

integers.

For example, dolichol originating from human liver is believed to consist of 0.9% of the compound wherein n is 16; 8.8% of the compound
5 wherein n is 17; 36.6% of the compound wherein n is 18; 37.7% of the compound wherein n is 19;
12.4% of the compound wherein n is 20; 3.2% of the compound wherein n is 21 and 0.7% of the compound wherein n is 22. On the other hand, dolichol
10 originating from swine liver is believed to consist of a small amount of the compound wherein n is 10; 2.5% of the compound wherein n is 16; 19.8% of the compound wherein n is 17; 43.5% of the compound wherein n is 18; 28.6% of the compound
15 wherein n is 19 and 5.5% of the compound wherein n is 20. Furthermore dolichol originating from yeast is believed to consist of 3.0% of the compound wherein n is 12; 14.1% of the compound wherein n is 13; 43.5% of the compound wherein n is 14; 34.5% of the compound wherein n is 15 and 4.8% of the compound wherein n is 16. Dolichol
20 to be used in the embodiments of the present invention may obviously include the dolichols as described above as well as those extracted from
25 other animal and vegetable tissues and having

various compositions.

The expression "dolichol phosphate" as used herein means an ester which is formed by bonding the terminal hydroxyl group of dolichol to phosphoric acid and has the following chemical structure:



wherein n represents an integer of 14 to 24 and m represents an integer of 1 to 3.

Similar to free dolichol, dolichol phosphate being used in the present invention may be a single compound wherein n is a particular integer or a mixture of compounds wherein n represents various integers.

The invention will be illustrated to the therapeutical effect below with reference to experimental examples. The effect to hyperuricuria is proved in Experimental Examples 1 and 2; that to hepatic diseases, in No. 3; that to diabetes, in Nos. 4 and 5; and that to hyperlipemia, in Nos. 6 and 7.

Experimental Example 1

60 mg/kg of Strepto Zotocin was injected to the tail vein of each male Sprague-Dawley rat of 140 to 160 g in body weight to thereby induce 5 hyperuricuria experimentally. Three days after the injection of Strepto Zotocin, 0.3 ml of a 1% dolichol/lecithin emulsion was injected into the femoral muscle of the rat once a day for four days. One day after the final administration, heparinized 10 blood was collected from the aorta under etherization. The heparinized blood was centrifuged at 3,000 r.p.m. for 10 min and then uric acid in the supernatant was determined.

Table 1 shows the result.

15

Table 1

Group	n	Uric acid
Normal rats not treated in the way as described in the Experimental Example 1	5	1.5 ± 0.19
Hyperuricuric rats treated in the way as described in the Experimental Example 1	5	2.9 ± 0.85*
Hyperuricuric rats administered 3 mg of dolichol as described in the Experimental Example 1	4	1.4 ± 0.22

25

Experimental Example 2

50 mg/kg of Strepto Zotocin was injected to the tail vein of each male Sprague-Dawley rat of 170 to 190 g in body weight to thereby induce 5 hyperuricuria experimentally. 10 days after the injection of Strepto Zotocin, 0.3 ml of a 1% dolichol monophosphate/lecithin emulsion was injected into the femoral muscle of the rat once a day for 42 days. One day after the final 10 administration, heparinized blood was collected from the aorta under etherization. The heparinized blood was centrifuged at 3,000 r.p.m. for 10 min and then uric acid in the supernatant was determined.

15

Table 2

Group	n	Uric acid
Hyperuricuric rats treated in the way as described in the Experimental Example 2	8	7.3 ± 5.4
Hyperuricuric rats administered 3 mg of dolichol monophosphate as described in the Experimental Example 2	8	1.8 ± 0.63*

The results of the Experimental Examples 1 and 2 clearly indicate that administration of dolichol or its phosphate would significantly lower high uric acid values in blood to a normal level.

5 Accordingly these compounds are extremely effective therapeutic and/or preventive agents for hyperuricuria.

The compounds of the present invention may be administered for treating and/or preventing 10 hyperuricuria such as gout either orally or parenterally, e.g., intramuscularly, hypodermically or intravenously.

Experimental Example 3. Effects of dolichol and its 15 phosphate on hepatic regeneration after hepatectomy.

(1) Method

Male Sprague-Dawley rat (7 weeks of age, each 210 to 240 g in body weight) were subjected to. hepatectomy according to the method reported by 20 Higgins and Anderson. That is, the rat had an abdominal operation under etherization to remove the right and left median lobes of liver (approximately 72 % on average). After saturation, the rat was fed with Oriental Solid Feed and tap water in a usual 25 manner. After a certain period, the rat was exsangu-

inated under etherization. Then the liver was weighed to calculate the hepatic regeneration rate by the following equation:

$$\frac{\text{Weight of regenerated liver} - \text{Weight of residual liver}}{5 \text{ Weight of removed liver}} \times 100$$

= Regeneration Ratio (%).

wherein the weight of residual liver was determined by subtracting the weight of the removed liver from the weight of the whole liver at the operation which 10 was regarded 4.65 g per 100 g of body weight.

(2) Effects of dolichol on the regeneration rate

30 mg/kg of a dolichol/lecithin emulsion was administered intraperitoneally to a rat once a day for 15 consecutive eight days (five days preoperation and three days post-operation). Table 3 shows the result.

Table 3

Group	n	Dose (mg/kg/day)	Regeneration rate (%)
Control group	14	—	40.81 ± 1.97
Dolichol-administered group	7	30	48.78 ± 1.54**

Table 3 indicates that continuous intraperitoneal administration of dolichol of the present invention at a dose of 30 mg/kg/day would significantly raise 25 the regeneration rate.

(3) Effect of dolichol phosphate on the regeneration rate

Three days after the hepatectomy, dolichol monophosphate was intravenously administered to a rat 5 followed by the evaluation after four days, i.e., seven days after the operation. Table 4 shows the result.

Table 4

Group	n	Dose (mg/kg/day)	Regeneration rate (%)	Total protein in blood (mg/dl)
Normal rats	2	-	-	6.35
Control	8	-	70.5 ± 2.0	5.8 ± 0.05
Dolichol phosphate	8	15	77.5 ± 5.2	6.1 ± 0.08*

Table 4 clearly indicates that an intravenous injection of dolichol phosphate after a posthepatectomic 15 increase in blood cholesterol would raise the regeneration rate and significantly increase the total protein content in blood.

The result of this Experimental Example teaches that dolichol and a phosphate 20 thereof according to the invention would accelerate the recovery of the function of hepatic cells at regeneration.

The compounds of the present invention are effective for treating and/or preventing hepatic 25 diseases such as inflammation, denaturation, necrosis, choleresis insufficiency and saccharometabolic disorder

caused by alcohol, malnutrition, viruses, chemical substances, toxins or the like.

Thus the compounds of the present invention are effective for treatment and/or preventing hepatic diseases including acute and chronic hepatitis and hepatocirrhosis.

Experimental Example 4

60 mg/kg of Strepto Zotocin was injected to the tail vein of each male Sprague-Dawley rat of 140 to 160 g in body weight to thereby induce diabetes experimentally. Three days after the injection of Strepto Zotocin, 10 μ l of whole blood was collected from the tail vein of the rat to determine blood sugar content by the glucose oxidase method. The rat showed blood sugar content not less than 250 mg/dl, which indicated that it suffered from diabetes. Three days after the injection of Strepto Zotocin, 0.3 ml of a 1 % dolichol/lecithin emulsion was injected to in the femoral muscle of the rat four times a day for four days. One month after the final administration, heparinized blood was collected from the aorta under etherization. The heparinized blood was centrifuged at 3,000 r.p.m. for 10 min and then triglyceride and glucose in the supernatant were determined.

25 Table 5 shows the results.

Table 5

Group	n	Triglyceride (mg/dl)	Glucose (mg/dl)
Normal rats not treated in the way described in the Experimental Example 4	5	101 ± 6	184 ± 10
Diabetic rats treated in the way as described in the Experimental Example 4	5	765 ± 277	548 ± 30
Diabetic rates administered 3 mg of dolichol as described in the Experimental Example 4	4	199 ± 54	477 ± 43

10

Experimental Example 5

50 mg/kg of Strepto Zotocin was injected to the tail vein of each male Sprague-Dawley rat of 170 to 190 g in body weight to thereby induce diabetes experimentally.

15 One day after the injection of Strepto Zotocin, 10 μ l of whole blood was collected from the tail vein of the rat to determine blood sugar content by the glucose oxidase method. The rat showed blood sugar content not less than 250 mg/dl, which indicated that it suffered 20 from diabetes. 10 days after the injection of Strepto Zotocin, 0.3 ml of a 1 % dolichol monophosphate/lecithin emulsion was injected into the femoral muscle of the rat once a day for 42 days. One day after the final administration, heparinized blood was collected from the

25

aorta under etherization. The heparinized blood was centrifuged at 3,000 r.p.m. for 10 min and then triglyceride and glucose in the supernatant were determined.

5

Table 6

Group	n	Triglyceride (mg/dl)	Glucose (mg/dl)
Diabetic rats treated in the way as described in the Experimental Example 4	8	2160 ± 1721	650 ± 108
Diabetic rats administered 3 mg of dolichol monophosphate as described in the Experimental Example 5	8	514 ± 361*	534 ± 64*

The results in Experimental Examples 4 and 5 clearly indicate that the administration of dolichol or its phosphate, i.e. the compounds of the present invention, significantly lower the content of both triglyceride and glucose.

Accordingly these compounds are extremely effective therapeutic and/or preventive agents for diabetes.

20

25

013

0149847

Experimental Example 6

60 mg/kg of Strepto Zotocin was injected to the tail vein of each male Sprague-Dawley rat of 140 to 160 g in body weight to thereby induce 5 hyperlipemia experimentally. Three days after the injection of Strepto Zotocin, 0.3 ml of a 1% dolichol/lecithin emulsion was injected into the femoral muscle of the rat once a day for four days. One month after the final administration, heparinized 10 blood was collected from the aorta under etherization. The heparinized blood was centrifuged at 3,000 r.p.m. for 10 min and then total protein (TP), albumin (Alb), total cholesterol (T-CHO) and tri-glyceride (TG) were determined.

15 Table 7 shows the results.

20

25

014

0149847

Table 7

Group	n	TP	Alb (g/dl)	T·ClO (mg/dl)	TG (mg/dl)
Normal rats not treated in the way as described in the Experimental Example 6.	5	5.9 ± 0.2	3.3 ± 0.09	66 ± 14	101 ± 6
Hyperlipemic rats treated in the way as described in the Experimental Example 6	5	5.6 ± 0.11*	2.9 ± 0.22*	172 ± 26***	765 ± 277**
Hyperlipemic rats administered 3 mg of dolichol as described in the Experimental Example 6	4	5.6 ± 0.23	3.0 ± 0.13	89 ± 11###	199 ± 54###

015

0149847

Experimental Example 7

50 mg/kg of Strepto Zotocin was injected to the tail vein of each male Sprague-Dawley rat of 170 to 190 g in body weight to thereby induce 5 hyperlipemia experimentally. 10 days after the injection of Strepto Zotocin, 0.3 ml of a 1% dolichol monophosphate/lecithin emulsion was injected into the femoral muscle of the rat once a day for 42 days. One day after the final administration, heparinized blood was collected from the 10 aorta under etherization. The heparinized blood was centrifuged at 3,000 r.p.m. for 10 min and then total cholesterol (T-CHO), triglyceride (TG), phospholipid (PL) and non-esterified fatty acid 15 (NEFA) in the supernatant were determined.

Table 8 shows the results.

Table 8

Group	n	T·C10 (mg/dl)	TG (mg/dl)	PL (mg/dl)	NEFA (mg/dl)
Hyperlipemic rats treated in the way as described in the Experimental Example 7	8	186 ± 49	2160 ± 1721	415 ± 102	2.60 ± 1.1
Hyperlipemic rats admini- stered 3 mg of dolichol monophosphate as described in the Experimental Example 7	8	82 ± 32***	514 ± 361	211 ± 78***	0.98 ± 0.43**

The results in Experimental Examples 6 and
7 clearly indicate that administration of
dolichol or its phosphate, i.e., the compounds of
the present invention would be effective for
5 treating hyperlipemia. Accordingly these compounds
serve as extremely effective lipometabolism
improvers and therapeutic and/or preventive agents
for arteriosclerosis accompanied with hyperlipemia.

Dolichol and its phosphate which are the
10 compounds of the present invention are highly safe.
Therefore it is possible to administer these com-
pounds continuously, which also make the present
invention very valuable.

For example, no death nor side effect were
15 observed when 1,500 mg/kg of dolichol i.e. the
compound of the present invention was orally
administered to SD rats of approximately 200 g
in body weight.

20

25

The dose depends on the stage of the disease or the age of the patients. These compounds may be administered usually in amounts of approximately 10 to 1,000 mg a day and preferably approximately 50 to 300 mg a day though without particular limitation.

The compounds of the present invention may be formulated in a well-known manner in the art into various forms such as tablets, granule, powder, capsules, injections and suppositories. These compounds may be formulated in a conventional manner by using conventional carriers.

For example, solid pharmaceuticals for oral administration may be prepared by adding an excipient with, if necessary, a binder, a disintegrant, a lubricant, a colorant, a corrigent or the like to the base and then formulating the mixture into a tablet, a coated tablet, granule, powder, capsule or the like in a conventional manner.

Examples of the excipient are lactose, corn

starch, white sugar, glucose, sorbitol, crystalline cellulose and silicon dioxide. Examples of the binder are polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, gum arabic,

5 tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone. Examples of the disintegrant are starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium

10 citrate, dextrin and pectin. Examples of the lubricant are magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. Any colorant which is pharmaceutically acceptable may be used. Examples of the corrigent are cacao

15 powder, menthol, aromatic powder, peppermint oil, borneol and cinnamon powder. The obtained tablet or granule may be coated with sugar, gelatin or the like if desired.

An injection may be prepared by adding

20 desired agents such as a pH adjustor, a buffer, a stabilizer and a solubilizing agent to the base and then formulating the mixture into a hypodermic, intramuscular or intravenous injection in a conventional manner.

Processes for preparing dolichol which is the compound of the present invention will be given for reference.

Preparative Example 1: Preparation of a pancreatic fat extract

5 1 kg of minced swine pancreas was stirred vigorously in 4 l of acetone to extract oil and fat components. The acetone phase was separated to obtain 4.2 l of a liquor. Then the liquor was concentrated under heating to obtain 500 ml of a
10 concentrate. After cooling the concentrate, a solidified fat phase called a pancreatic fat extract (100 g) was separated.

Preparative Example 2: Preparation of a pancreatic fat extract

15 2.5 kg of minced swine pancreas was stirred vigorously in 10 l of ethanol to extract oil and

fat components. The alcoholic phase was separated to obtain 10.1 l of a liquor. Then the liquor was concentrated under heating to obtain 1.5 l of a concentrate. After cooling the concentrate, a
5 solidified fat phase called a pancreatic fat extract (280 g) was separated.

Preparative Example 3: Preparation of a pancreatic fat extract

200 ml of water, 100 g of swine duodenum
10 (10 g of pancreatin) and 10 ml of a 40% NaOH solution were added to 1 kg of minced swine pancreas. Then the mixture was thoroughly stirred at pH 8.5 and subjected to the activating treatment which was employed in the activation of protease
15 or in preparing pancreatin.

Subsequently 4.8 l of acetone was added to the mixture to extract oil and fat components. Then the acetone phase (5.3 ml) was separated.

The precipitate was further defatted and
20 ground to obtain 220 g of pancreatin.

The acetone phase was concentrated under heating to obtain 700 ml of a concentrate. After cooling the concentrate, a solidified fat phase called a pancreatic fat extract (100 g) was
25 separated.

Preparative Example 4: Preparation of a pancreatic fat extract

3 kg of minced swine pancreas was stirred vigorously in 12 l of a 30% ethanol solution (pH 3.0). Then the alcohol/aqueous phase (13 l) was concentrated under heating to obtain 5 l of a concentrate. After cooling the concentrate, 250 g of a solidified pancreatic extract was obtained.

In addition, an intense insulin activity was observed when the liquid phase was administered intraperitoneally to a rat to examine its effect of lowering blood sugar.

Preparative Example 5:

1.5 kg of the pancreatic fat extract prepared in the Preparative Example 1 was dissolved in 3 l of methanol. Then 1.7 kg of a 15% aqueous solution of caustic soda was added dropwise to the solution at room temperature under stirring. The mixture was saponified for one hour at 60 to 70°C and then cooled to 50°C. Subsequently the mixture was extracted with 3 l of hexane. The organic phase was washed with 1 l of a solvent mixture (methanol/water 2 : 1) and allowed to stand at 4°C overnight. Precipitated crystals were filtered and the filtrate was concentrated. Then the

obtained concentrate was purified with silica gel column chromatography by using n-hexane/benzene as an eluent. Consequently 85 mg of dolichol in the form of a colorless oil was obtained. The 5 dolichol prepared in the present Example was identified since the retention time thereof in HPLC coincided with that of a commercial dolichol (Sigma Co., INC. D-4511).

HPLC: stationary phase: nucleosil C₁₈ 7μ x 25 cm,
10 mobile phase: a solvent mixture consisting
of 520 parts of isopropyl
alchol, 240 parts of methanol,
40 parts of n-hexane and 18
parts of water,
15 flow rate: 1 ml/min,
detection wavelength: 210 nm.

Now a Formulation Example in which dolichol which is the compound of the present invention and referred to as the base in the Example is used as 20 an active ingredient will be given.

Formulation Example: Tablets

base	10 g
silicic anhydride	50 g
crystalline cellulose	70 g
25 corn starch	36 g

024

0149847

hydroxypropylcellulose 10 g

magnesium stearate 4 g

The mixture was formulated into tablets each
weighing 180 mg in a conventional manner.

5

10

15

20

25

025

0149847

CLAIMS:

1. A use of dolichol or a phosphate thereof as a therapeutically treating and preventive agent.

5 2. A use as claimed in Claim 1 for treating and preventing hyperuricuria, hyperlipemia, arteriosclerosis, diabetes or hepatic diseases or improving lipometabolism.

10

15

20



Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number:

O 149 847
A3

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: **84116353.8**

(51) Int. Cl.³: **A 61 K 31/045**
A 61 K 31/66

(22) Date of filing: **27.12.84**

(30) Priority: **26.12.83 JP 244227/83**
26.12.83 JP 244228/83
26.12.83 JP 244229/83
26.12.83 JP 244230/83

(43) Date of publication of application:
31.07.85 Bulletin 85/31

(88) Date of deferred publication of search report: **08.11.89**

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI NL SE

(71) Applicant: **Eisai Co., Ltd.**
6-10, Koishikawa 4-chome Bunkyo-ku
Tokyo 112(JP)

(72) Inventor: **Yamatsu, Isao**
3605-699, Kashiwada Ushikumachi
Inashiki-gun Ibaragi(JP)

(72) Inventor: **Suzuki, Takeshi**
56-107, Sakae-cho 1 chome Ushikumachi
Inashiki-gun Ibaragi(JP)

(72) Inventor: **Abe, Shinya**
40-2, Ohaza-Shiroyama Kukizakimura
Inashiki-gun Ibaragi(JP)

(72) Inventor: **Nakamoto, Kouji**
712-91, Itaya-cho Nakanuki
Tsuchiura-shi Ibaragi(JP)

(72) Inventor: **Kajiwara, Akiharu**
29-4, Higashi-Arai Yatabemachi
Tsukuba-gun Ibaragi(JP)

(72) Inventor: **Katayama, Kouichi**
2-33, Umezono Sakuramura
Niihari-gun Ibaragi(JP)

(72) Inventor: **Tsunoda, Hajime**
10-4, Toukoudai 1 chome Toyosatomachi
Tsukuba-gun Ibaragi(JP)

(72) Inventor: **Murakami, Manabu**
6-8, Toukoudai 1 chome Toyosatomachi
Tsukuba-gun Ibaragi(JP)

(72) Inventor: **Ono, Hideki**
23-30, Umezono 2 chome Sakuramura
Niihari-gun Ibaragi(JP)

(72) Inventor: **Yamada, Kouji**
15-19, Toride 2 chome
Toriode-shi Ibaragi(JP)

(74) Representative: **Hansen, Bernd, Dr.rer.nat. et al,**
Hoffmann, Eitze & Partner Patentanwälte Arabellastrasse
4 Postfach 81 04 20
D-8000 München 81(DE)

(54) Therapeutic and preventive agent containing dolichol.

(55) Dolichol or phosphate thereof is useful as a therapeutically treating and preventive agent, in particular, for hyperuricuria, hyperlipemia, diabetes and hepatic diseases.

EP 0 149 847 A3

0149847

European Patent
Office

EUROPEAN SEARCH REPORT

Application number

EP 84 11 6353

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, vol. 179, no. 634, 1977; Academic Press Inc. R.W. KEENAN et al.: "The tissue and subcellular distribution of (3H)do-lichol in the rat" * Whole article * --	1	A 61 K 31/045 A 61 K 31/66
X	US-A-4 325 974 (YAMATSU et al.) * Claim 5 * -----	1	
TECHNICAL FIELDS SEARCHED (Int. Cl.4)			
A 61 K			
X			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	13-04-1989	GERLI	
CATEGORY OF CITED DOCUMENTS			
<input checked="" type="checkbox"/> particularly relevant if taken alone <input checked="" type="checkbox"/> particularly relevant if combined with another document of the same category <input checked="" type="checkbox"/> technological background <input type="checkbox"/> non-written disclosure <input type="checkbox"/> intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document			



European Patent
Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

- All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.
- Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid.
namely claims:
- No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,
namely:

1. Claim 1: Use of dolichol for the preparation of a medicament with therapeutical and preventive activity
2. Claim 2: Use of dolichol for the preparation of a medicament for the treatment of hyperuricuria
3. Claim 2: Use of dolichol for the preparation of a medicament for the treatment of hyperlipidemia + atherosclerosis + improving lipometabolism
4. Claim 2: Use of dolichol for the preparation of a medicament for the treatment of diabetes
5. Claim 2: Use of dolichol for the preparation of a medicament for the treatment of hepatic diseases

- All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.
- Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid.
namely claims:
- None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims.

namely claims: 1

THIS PAGE BLANK